THE INFLUENCE OF A FAMILY HISTORY OF ASTHMA AND PARENTAL SMOKING ON AIRWAY RESPONSIVENESS IN EARLY INFANCY

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Abstract *Background.* Airway responsiveness to inhaled nonspecific bronchoconstrictive agents has been demonstrated in normal, healthy infants. However, it is unknown whether airway responsiveness is present from birth or if it develops as a result of subsequent insults to the respiratory tract. To investigate this question, we assessed airway responsiveness in 63 normal infants at a mean age of 4½ weeks.

Methods. Respiratory function was measured with use of the partial forced expiratory flow–volume technique to determine the maximal flow at functional residual capacity ($\dot{V}_{maxFRC}$). The infants inhaled nebulized histamine at sequentially doubled concentrations (0.125 to 8.0 g per liter), until a concentration was reached at which the $\dot{V}_{maxFRC}$ fell by 40 percent from the base-line value (PC_{40}) or until a concentration of 8.0 g per liter was reached. We also assessed maternal serum levels of IgE, cord-serum levels of IgE, the infants' skin reactivity to several allergens, and the parents' responsiveness to histamine and obtained family histories of asthma and smoking.

Results. Airway responsiveness was increased in infants with a family history of asthma (n = 19; median PC_{40}, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; P<0.01), parental smoking (n = 13; median PC_{40}, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; P<0.05), or both (n = 20; median PC_{40}, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; P<0.05), as compared with the infants with no family history of asthma or smoking. The infants with no family history of asthma or smoking had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00). No significant relations were detected between the immunologic variables and the PC_{40} in the infants.

Conclusions. This study indicates that airway responsiveness can be present early in life and suggests that a family history of asthma or parental smoking contributes to elevated levels of airway responsiveness at an early age. (N Engl J Med 1991; 324:1168-73.)

ALTHOUGH asthma is considered to result from a complex interaction of genetic and environmental influences, there has been little recent progress in determining their relative contributions.[1] Recent developments in the measurement of respiratory function in infants[2] have allowed inhalation challenges to be used in this age group in order to obtain objective measurements of airway responsiveness (the ability of the airways to constrict in response to certain stimuli).[3] This technique is of particular interest, since airway responsiveness is the most useful objective physiologic measurement associated with the presence of asthma.[1]

The first inhalation-challenge studies in older normal infants, in which investigators used methacholine,[4] cold, dry air,[5] or histamine,[6] indicated that airway responsiveness was present in infants during the first year of life. Two questions have arisen from these studies. First, how early in infancy is airway responsiveness present? It has been speculated that persons with asthma are not born with heightened airway responsiveness but are born with a tendency to increased responsiveness after an insult to the respiratory system.[1,7] Second, is the initial level of airway responsiveness the same for all infants, or do genetic or environmental influences, or both, result in differing levels of responsiveness at birth? Specific environmental features, such as viral infections, irritants, and allergens, affect airway responsiveness in older children and adults,[1] but their influence on airway responsiveness in infants is unknown.

To investigate these two questions, we undertook a prospective, longitudinal study to determine the presence and level of airway responsiveness and its relation to a family history of asthma or parental smoking in 63 normal infants. This report presents our findings at the first assessment of the infants, at a mean age of 4½ weeks.

METHODS

Subjects

Sixty-three infants, 24 girls and 39 boys, were studied at a mean age of 4½ weeks (range, 2 to 10). The criteria for inclusion were full-term gestation and an absence of perinatal problems and major congenital anomalies. At the time of the assessment, none of the infants had previously had a lower respiratory tract infection or any clinically important nonrespiratory illness. No infant had had an upper respiratory tract infection in the preceding three weeks. All infants were well at the time of the study.

The families of all the infants were recruited randomly at the prenatal clinic at Osborne Park Hospital, Perth, Western Australia. This is a peripheral metropolitan hospital with 2000 deliveries per year. The recruitment procedure began with an interview with the mother during a routine prenatal visit, at which time she was given written information on the family involvement that would be required during the proposed 12-month study period. One week after the interview, each family was contacted by telephone to determine whether they would agree to participate in the study. Signed parental consent was obtained for all infants. Over a 12-month period, 241 mothers were interviewed and 63 (26 percent) consented to participate. The study was performed with the approval of the medical ethics committees of Princess Margaret Hospital and the University of Western Australia.

Details of respiratory illness and atopy in the family and parental smoking habits were obtained with use of a modified American

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Thoracic Society questionnaire[8] administered by a single investigator. The 63 infants were divided into four groups on the basis of their family histories of asthma and parental smoking. Those classified as having a family history of asthma were those whose parents reported asthma in primary relatives (the parents and siblings of the infant) or secondary relatives (grandparents, aunts, and uncles). Infants with a family history of smoking were those whose parents reported that either or both had smoked during the pregnancy. The four groups were defined as follows: group 1 (n = 11) — no family history of asthma in primary or secondary relatives, both parents nonsmokers; group 2 (n = 19) — family history of asthma in primary or secondary relatives (or both), both parents nonsmokers; group 3 (n = 13) — no family history of asthma in primary or secondary relatives, one or both parents smoked during the pregnancy; and group 4 (n = 20) — family history of asthma in primary or secondary relatives (or both), one or both parents smoked during the pregnancy. The responses to questions about parental smoking habits after the infant's birth indicated that all parents in groups 1 and 2 remained nonsmokers and the smoking parents in one family in group 3 and one in group 4 ceased smoking after the birth of the infant.

Assessment

Responsiveness to histamine was measured in 75 of the parents by the rapid-inhalation technique of Yan et al.[9] To assess immunologic influences on airway responsiveness, IgE was measured in maternal and cord serum[10] by the Clinical Immunology Research Unit, Princess Margaret Hospital for Children. Forty-seven pairs of samples of maternal and cord serum were analyzed.

Respiratory function was assessed by the forced expiratory flow-volume method.[7] A jacket was rapidly inflated at end inspiration, and flow was measured from the partial expiratory flow–volume curve at functional residual capacity. The jacket pressure was gradually increased over a series of forced expirations until maximal flow at functional residual capacity ($\dot{V}_{max_{FRC}}$) was obtained. Flow was measured with a No. 1 Fleisch pneumotachygraph (PK Morgan, Chatham, England), a Validyne DP-45 pressure transducer (Northridge, Calif.), and a Validyne CD19 amplifier. Volume values were obtained by electronic integration. The infant breathed through a molded-putty face mask attached to the pneumotachygraph. All signals were recorded on a chart recorder (Linearecorder F Wr 3801, Graphtec, Tokyo); flow and volume were monitored during the study with a Tektronix 5223 digitalizing storage oscilloscope (Beaverton, Oreg.) and recorded on tape (TEAC SR-50, TEAC Corp., Tokyo). Taped signals were transcribed to paper on a Hewlett-Packard 7090A x,y paper plotter (Waltham, Mass.). Arterial oxygen saturation was monitored throughout the study with a Nellcor N-200 E pulse oximeter (Hayward, Calif.). Supplementary oxygen was administered if arterial oxygen saturation fell below 90 percent.

Infants were studied while asleep after they were given a dose of chloral hydrate (80 mg per kilogram of body weight). The minimal jacket pressure required to produce $\dot{V}_{max_{FRC}}$ was established. This pressure was used in all subsequent forced expirations. Respiratory function was assessed before and after the administration of nebulized saline with an Airlife nebulizer (American Pharmaseal, Valencia, Calif.) at 6 liters per minute. This and all other nebulized agents were delivered directly to the face mask and inhaled during one minute of tidal breathing. For the base-line $\dot{V}_{max_{FRC}}$, we used the mean of the values for five forced expirations after the administration of nebulized saline.

The histamine challenge was carried out by administering sequentially doubling concentrations of nebulized histamine, ranging from 0.125 g per liter to a maximal concentration of 8.0 g per liter, as previously described.[6] A new concentration was delivered every five minutes, and respiratory function was assessed after each, with a minimum of five forced expirations at each measurement. The challenge was ended when a response to histamine was recorded or when the maximal concentration was reached. A response was defined as a decrease in the mean $\dot{V}_{max_{FRC}}$ of at least 40 percent from the base-line value. For infants who responded to histamine, the concentration that provoked a 40 percent decrease in $\dot{V}_{max_{FRC}}$ (PC_{40}) was derived by linear interpolation from the plot of the log histamine concentration against the percent decrease in $\dot{V}_{max_{FRC}}$ from base line. The coefficient of repeatability for a histamine challenge to an infant according to this protocol was 3.3 sequentially doubled concentrations.[11] We also determined the dose of histamine that provoked a 20 percent decline in the forced expiratory volume in one second in the parents (PD_{20}).

Two investigators measured airway function and determined airway response; one, who operated the equipment, was blinded to the infant's family history; the second, who recorded data on the infant's chart, had recruited the participants and completed the family-history questionnaires and was therefore aware of the family history. Because the blinded investigator identified changes in pulmonary function, no bias was introduced into the results.

Skin reactivity was assessed in all infants on the same day as, but before, the administration of chloral hydrate and the subsequent histamine challenge. The allergens used were *Dermatophagoides farinae*, perennial ryegrass pollen, cow's milk, and egg white (Hollister-Stier, Elkhart, Ind.). A positive response was defined as a wheal 2 mm or more in diameter.

Statistical Analysis

Differences in base-line values for $\dot{V}_{max_{FRC}}$ and PC_{40} among the groups were analyzed with use of the Mann–Whitney U test.[12] The median and confidence intervals for the median were determined with use of the Confidence Interval Analysis microcomputer program.[13,14] All values for IgE underwent logarithmic transformation before analysis. Within each family-history group, regressions were used to determine the relation between maternal serum IgE levels and cord-serum IgE levels, maternal serum IgE levels and PC_{40}, and cord-serum IgE levels and PC_{40}. Maternal serum and cord-serum IgE levels in the groups were compared with use of Student's unpaired (two-tailed) t-test.

Results

Descriptive data for the groups of infants are shown in Table 1. The infants in group 3 had a significantly lower mean birth weight than those in groups 2 and 4. All the mothers of infants in group 3 smoked during the pregnancy. Among the infants in group 4, 16 had mothers who had smoked during the pregnancy and 4 had fathers who had smoked during this time. There were no significant differences between the birth weights of infants in group 4 whose mothers had

Table 1. Characteristics of the Subjects According to Family-History Group.*

Group	Birth Weight	Weight†	Length†	Age†	Sex (F:M)
	kg	kg	cm	wk	
Group 1 (n = 11)	3.4±0.5	4.8±0.5	54.1±2.7	3.8±1.9	6:5
Group 2 (n = 19)	3.6±0.5‡	5.1±0.7	55.1±2.8	4.8±2.2	6:13
Group 3 (n = 13)	3.1±0.4	4.7±0.9	53.8±3.2	4.5±2.2	5:8
Group 4 (n = 20)	3.5±0.5§	4.8±0.7	54.3±2.7	4.6±1.9	7:13

*Plus–minus values are means ±SD. Infants in group 1 had no family history of smoking or asthma; those in group 2 had a family history of asthma but neither parent smoked; those in group 3 had no family history of asthma and at least one parent who smoked; and those in group 4 had a family history of asthma and at least one parent who smoked.

†At the time of the study.

‡$P<0.005$ for the comparison with group 3.

§$P<0.05$ for the comparison with group 3.

smoked and those of infants whose fathers (but not their mothers) had smoked or those of the infants in groups 1 and 2.

Base-line lung function for the groups is shown in Figure 1. Base-line $\dot{V}_{maxFRC}$ is expressed as a percentage of the predicted value, which was based on the predictive equation of Tepper et al.[15] The four groups did not differ significantly in base-line lung function.

Figure 2 shows the responsiveness to histamine in the four groups. Individual values for PC_{40} are given, along with the median value of PC_{40} for each group. Infants who responded to the first concentration were classified as having a PC_{40} of less than 0.125 g per liter. Those who had not responded at a concentration of 8.0 g per liter were classified as having a PC_{40} of more than 8.0 g per liter. PC_{40} values were not obtained for three infants; two were flow-limited at base line (i.e., forced expiratory flow was no greater than tidal expiratory flow) and therefore were not challenged with histamine (both in group 2), and in the case of one infant in group 4, the challenge was discontinued when upper-airway obstruction developed. Infants in group 1, who had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00), were significantly less responsive than those in group 2 (median PC_{40}, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; $P<0.01$), group 3 (median PC_{40}, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; $P<0.05$), and group 4 (median PC_{40}, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; $P<0.05$). There were no significant differences among the values for PC_{40} in groups 2, 3, and 4.

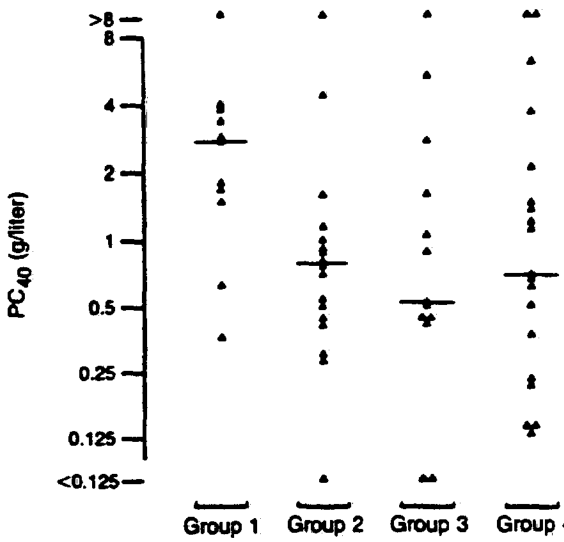

Figure 2. Individual Values for the Histamine Concentrations That Provoked a Decrease of 40 Percent in $\dot{V}_{maxFRC}$ (PC_{40}).

The groups were defined as in Figure 1. The horizontal lines show the median PC_{40} for each group. Two infants in group 2 had base-line flow limitation and therefore could not be challenged with histamine. No PC_{40} value could be determined for one infant in group 4, in whom excessive upper-airway noise developed, necessitating discontinuation of the challenge.

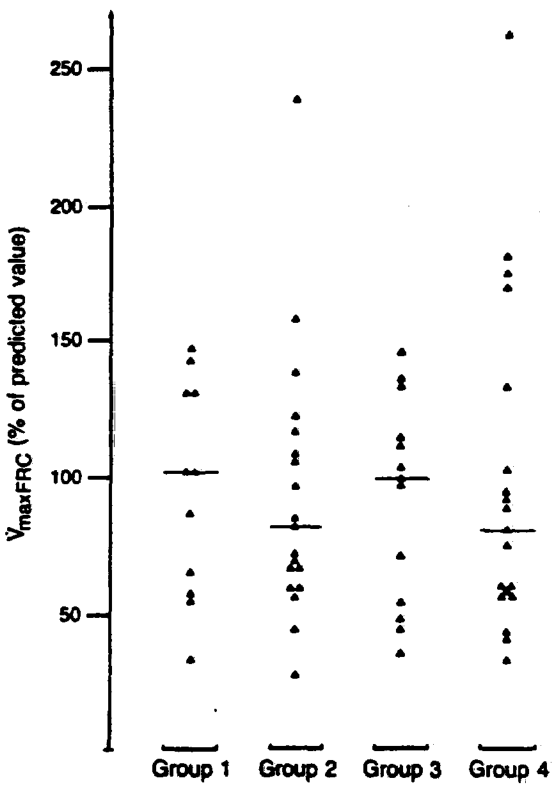

Figure 1. Individual Base-Line Values for $\dot{V}_{maxFRC}$, Expressed as a Percentage of the Predicted Value for Each Group.

The groups were defined as follows: group 1 — no family history of asthma, both parents nonsmokers; group 2 — family history of asthma, both parents nonsmokers; group 3 — no family history of asthma, one or both parents smoked; group 4 — family history of asthma, one or both parents smoked. The horizontal lines show the median percentage of predicted $\dot{V}_{maxFRC}$ for each group. Predicted values, derived with the predictive equation of Tepper et al.,[15] are based on the infants' heights; since one infant's height was not measured, only 19 data points are shown.

Of the 33 infants who had one or more parents who smoked during the pregnancy (groups 3 and 4), only 4 had fathers who smoked and nonsmoking mothers. All four were in group 4, where a family history of asthma was also present. We were therefore unable to determine the effect of paternal smoking alone.

Because there were more boys than girls in the group as a whole and because there was a particular disproportion in groups 2 and 4, comparisons of airway function were made on the basis of sex. No significant differences were found in either base-line lung function or airway responsiveness between boys and girls in the entire group of 63 infants or within the four family-history groups.

Of the 63 infants in whom skin reactivity was assessed, 7 had a positive response to one allergen and 1 had a positive response to two allergens. Responses were recorded for each of the four allergens and

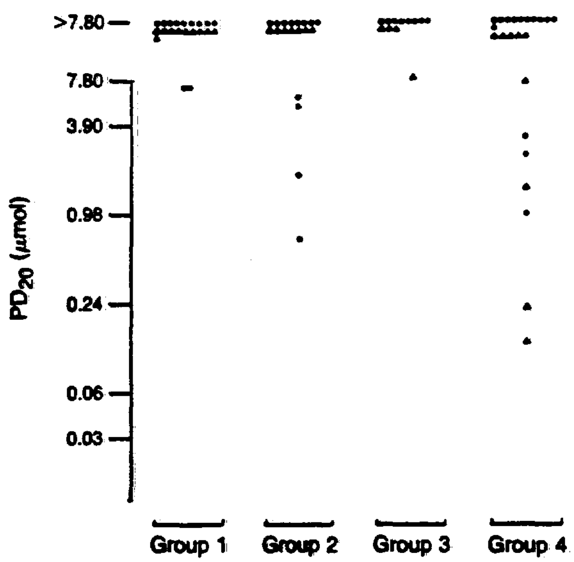

Figure 3. Doses of Histamine That Provoked a Decrease of 20 Percent in the Forced Expiratory Volume in One Second in 75 Parents of Infants in the Four Groups (PD_{20}).

The groups were defined as in Figure 1. Circles indicate mothers, and triangles fathers.

among infants in all four groups. There was no relation between the incidence of skin reactivity and the degree of responsiveness at this age.

Fourteen of the 75 parents who were tested responded to inhaled histamine. The distribution and level of response (PD_{20}) for parents of infants in each of the four groups are shown in Figure 3. There was no relation between the level of parental responsiveness to histamine and the infant's PC_{40}.

For the group as a whole, a significant positive correlation was found between the maternal serum IgE level and the cord-serum IgE level ($P<0.01$). When each family-history group was analyzed separately, however, this relation was not observed. No significant correlations were found between the maternal serum IgE level and the infant's value for PC_{40} or between the cord-serum IgE level and PC_{40}, either for the entire group of 63 infants or for the four family-history groups. There were no significant differences among the groups in either maternal venous serum IgE levels or cord-serum IgE levels (Fig. 4).

Discussion

The results of this study demonstrate that airway responsiveness to inhaled histamine is present in many normal, healthy infants soon after birth. We also found that the level of airway responsiveness in early life was increased if there was a family history of asthma, parental smoking, or both.

The development of techniques for assessing airway function in infants has made possible the study of airway responsiveness in the first two years of life, a period during which children had not been studied previously. Prendiville et al.[3] showed that infants with recurrent wheeziness were responsive to inhaled histamine. This study was followed by the work of Tepper with methacholine,[4] Geller et al. with cold, dry air,[5] and Le Souëf et al. with histamine,[6] which demonstrated that the airways of normal, healthy, asymptomatic infants were responsive to the same bronchoconstrictive agents routinely used in testing older children and adults. In these studies,[4-6] infants were studied well into the first year of life, at mean ages of 8.1 months, 5.6 months, and 7.8 months, respectively. We wished to investigate whether airway responsiveness could be detected in very early infancy. Therefore, in this study we assessed infants at a mean age of 4½ weeks, with some only 2 weeks old. A response to histamine was observed in all but 5 of the 63 infants. This finding indicates clearly that airway responsiveness is present very early in life, and it is not unreasonable to suggest that it may be present from birth.

Another reason for studying infants so early in life is that with increasing age the effect of a number of environmental insults to the airway is likely to increase. These irritants include exposure to cigarette smoke, exposure to allergens, and respiratory tract infections. These respiratory insults are known to increase airway responsiveness in older children and adults,[1] and it is possible that they also affect airway responsiveness in infants. Therefore, when airway responsiveness is assessed in middle-to-late infancy, exposure to these environmental factors makes it difficult to extrapolate the initial level of airway responsiveness. Studying infants soon after birth should help to minimize, but will not eliminate, this problem.

We found that the level of responsiveness to histamine in infants was related to the presence or absence of a family history of asthma. This finding suggests that the initial level of airway responsiveness may be genetically determined. A genetic effect on airway responsiveness in later life has been established in studies of twins[16] and of the families of persons with asth-

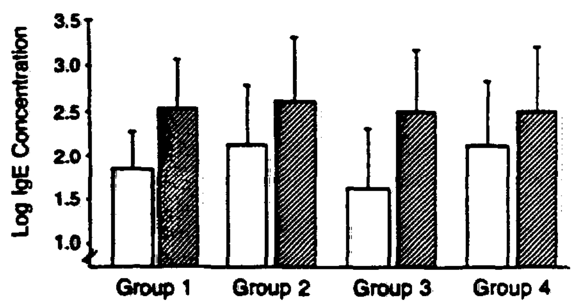

Figure 4. IgE Levels in Cord and Maternal Venous Serum, According to Family-History Group.

The groups were defined as in Figure 1. Open bars indicate mean cord-serum levels, and hatched bars mean maternal venous-serum levels. The T bars indicate the standard deviation.

ma.[17-19] Studies have shown a higher concordance for asthma and atopy in monozygotic twins than in dizygotic twins.[16] Furthermore, other studies have shown a significant relation between a history of asthma in parents and siblings and the development of asthma in early childhood.[18,19] Our study indicates that a history of asthma in primary or secondary relatives, or both, influences the level of airway responsiveness at an early age.

We also found that airway responsiveness was increased in infants whose parents reported smoking during the pregnancy. Population-based studies of airway responsiveness have found an increase in airway sensitivity among children with asthma whose mothers smoked. Martinez et al.[20] recently reported that exposure to tobacco smoke enhanced airway responsiveness in nine-year-old children; bronchial hyperresponsiveness was present in 70 percent of the children whose mothers smoked regularly during the pregnancy, but in only 29 percent of the children whose parents did not smoke during the pregnancy. Since these investigators did not find an overall association between airway responsiveness and current smoking by the mother, they suggested that fetal exposure to tobacco smoke may have had an important effect on airway responsiveness. Our study also demonstrates an association between parental smoking and the level of airway responsiveness in early infancy, although we are unable to separate the effects of prenatal and postnatal exposure to cigarette smoke. The effect of continued postnatal exposure on the base-line level of responsiveness and on the subsequent development of the symptoms of asthma is unknown. Moreover, we have not reported the amount of smoking, since it is widely recognized that the relation between the level of smoking reported by parents and the actual level of passive smoking by the fetus or infant is poor because of underreporting by parents, variations in ventilation in rooms and houses, and differences in the distance between the smoker and the infant.

Base-line lung function, expressed as a percentage of the predicted $\dot{V}_{maxFRC}$,[15] did not differ significantly among the four family-history groups, and no correlation was observed between base-line lung function and PC_{40}. These findings are in agreement with those of studies in humans[21-23] and animals[24,25] that have suggested that the caliber of the airway at base line may not be an important factor in responsiveness.

Many studies have been conducted to determine the usefulness of serum IgE levels measured at birth and during infancy in predicting the development of atopic diseases, including asthma, and skin reactivity.[26-31] These studies have indicated that a high IgE level is, in general, associated with atopy; however, all investigators have noted a wide range of IgE levels, with considerable overlap, between subjects with and without atopy. In our study, the infant's IgE level did not predict the initial level of airway responsiveness or skin reactivity, either for the group as a whole or for the four family-history groups individually. This lack of relation between atopic markers and airway responsiveness may be due to the fact that the infants were assessed before sufficient exposure to allergens had occurred. Bryant and Burns,[32] in a study of the relation between atopic status and airway responsiveness to histamine, found no correlations between serum IgE levels and the number of positive skin-prick responses or the level of airway responsiveness in a group of adults with asthma and normal adults.

Correlations have previously been found both between IgE levels in parents and those in infants[26] and between a family history of atopic diseases and the infant's IgE level.[26-31,33] We found a significant positive correlation between maternal and cord-serum IgE levels for the group as a whole, but these two measures did not discriminate among infants with different family histories. These data suggest that allergic markers are not strongly related to the initial level of airway responsiveness at this age. Because these infants are part of a longitudinal study, the potential role and relative importance of these immunologic markers may be clarified as they grow older.

In summary, we found that airway responsiveness to inhaled histamine was often present in normal, healthy, asymptomatic infants early in life. We suggest that responsiveness is present from birth and is determined both by inheritance and by exposure to parental cigarette smoking. The relation of this initial level of airway responsiveness to future levels of responsiveness, respiratory problems, and immunologic markers after exposure to environmental insults during infancy remains to be clarified.

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